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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,418	05/13/2005	Edouard S.P Bouvier	60009US(49991)	4955

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EDWARDS & ANGELL, LLP  
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EXAMINER
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ARNOLD, ERNST V

ART UNIT	PAPER NUMBER
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1616

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/26/2007	PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

<b>Office Action Summary</b>	Application No. 10/516,418	Applicant(s) BOUVIER ET AL.	
	Examiner Ernst V. Arnold	Art Unit 1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 13 February 2007.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-45, 62-65, 95-101, 106-113 and 117 is/are pending in the application.
- 4a) Of the above claim(s) 10, 31, 32, 34-45, 62-65, 95-101, 106-113 and 117 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-9, 11-30 and 33 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 29 November 2004 is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>11/29/04, 12/22/05, 10/5/06</u> . | 6) <input type="checkbox"/> Other: _____  |

### DETAILED ACTION

Claims 1-45, 62-65, 95-101, 106-113 and 117 are pending.

Claims 46-61, 66-94, 102-105, 114-116 and 118-122 have been cancelled.

Applicant elected Group I, claims 1-33 and further elected without traverse the species:

1) a proteolytic protein as the biomolecule; 2) biological fluids as the biological sample; 3) mass spectrometry as the type of analysis; 4) surfactant is degraded; 5) trypsin as the protease; and 6) SDS is absent in the response filed on 2/13/07.

Claims 1-9, 11-30 and 33 read on the species. Claims 10, 31, 32, 34-45, 62-65, 95-101, 106-113 and 117 have been withdrawn from consideration as being drawn to non-elected subject matter. The Examiner again notes for the record the inconsistency of claim 58, which has a status of 'original' but is included with cancelled claims 46-61.

Claims 1-9, 11-30 and 33 are presented for examination.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, 11-30 and 33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of enhancing the solubility of the proteins BSA, lysozyme, ovalbumin, myoglobin, ubiquitin and bacteriorhodopsin, does not reasonably provide enablement for a method of enhancing any chemical reaction of any molecule. **Thus, there are two enablement problems: 1) any chemical reaction and 2) any molecule.** Applicant is only

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enabled for: 1) enhancing the solubility (chemical reaction) of 2) the proteins BSA, lysozyme, ovalbumin, myoglobin, ubiquitin and bacteriorhodopsin (molecule). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims without an undue amount of experimentation.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: 1) scope or breadth of the claims; 2) nature of the invention; 3) relative level of skill possessed by one of ordinary skill in the art; 4) state of, or the amount of knowledge in, the prior art; 5) level or degree of predictability, or a lack thereof, in the art; 6) amount of guidance or direction provided by the inventor; 7) presence or absence of working examples; and 8) quantity of experimentation required to make and use the claimed invention based upon the content of the supporting disclosure. When the above factors are weighed, it is the Examiner's position that one skilled in the art could not practice the invention without undue experimentation.

1) Scope or breadth of the claims

The claims are broader in scope than the enabling disclosure. The specification merely discloses, without more, that a method of enhancing the solubility of proteins. However, Applicant is purporting to a method of enhancing any chemical reaction of any molecule.

2) Nature of the invention

The nature of the invention is directed to methods of solubilizing proteins with a dioxolan surfactant.

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3) Relative level of skill possessed by one of ordinary skill in the art

The relative level of skill possessed by one of ordinary skill in the art of chemical research is relatively high, as a majority of lead investigators directing scientific research and development in this particular technological area possess an Ph.D. in a scientific discipline such as organic synthetic chemistry, polymer chemistry, medicinal chemistry, biochemistry, pharmacology, biology or the like.

4) State of, or the amount of knowledge in, the prior art

The art teaches that dioxolans of the instant invention are useful for solubilizing proteins (See claims 27-31 in Lee et al. WO 00/70334). Edquist (US 2,093,958) teaches the use of copper ammonium cyanide to dissolve gold (column 1, lines 10-11 and 40-43).

5) Level or degree of predictability, or a lack thereof, in the art

The art teaches that not all proteins may completely dissolve in the presence of surfactants. Grabski et al. teach that some proteins such as histones and membrane proteins may not completely dissolve by heating in SDS sample buffer alone and may require addition of 6-8 M urea or a nonionic detergent such as Triton X-100 (Page 12 top left column). Thus, not all proteins are soluble in surfactants and various surfactant combinations may be required to solubilize some proteins.

6) Amount of guidance or direction provided by the inventor

Applicant was required to provide in the specification additional guidance and direction with respect to how use the claimed subject matter in order for the application to be enabled with respect to the full scope of the claimed invention. Although the instant specification discloses that a method of enhancing the solubility of the proteins BSA, lysozyme, ovalbumin, myoglobin,

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ubiquitin and bacteriorhodopsin (See Example 3, page 25 and page 26, Table 2 of the specification) with the claimed dioxolan surfactant ALS, it remains silent on enhancing any chemical reaction with any molecule with the surfactant.

7) Presence or absence of working examples

The specification fails to provide scientific data and working embodiments with respect to enhancing any chemical reaction with any molecule with the surfactant. The terms “chemical reaction” and “molecule” are too broad with respect to the disclosed scope and include such things as photo-oxidation, nuclear decay and isomerization for the chemical reactions and any molecule under the sun. However, Applicant has only shown solubilized proteins in Example 3, page 25 and Table 2 on page 26. The art teaches copper ammonium cyanide to dissolve gold and not the instant dioxolan surfactant.

8) Quantity of experimentation required to make and use the claimed invention based upon the content of the supporting disclosure

One of ordinary skill in the art would have to conduct a myriad number of experiments comprising picking and choosing amongst a tremendous number of chemical reactions that any molecule could undergo, designing experiments to measure the reaction feature, treating the molecule with the surfactant and measuring the result as compared to the reaction without the surfactant. It would take years to figure this out. And as shown above, not all proteins are soluble in surfactant solutions and some materials, gold, require special dissolution solutions. As a result, one of ordinary skill in the art would be required to conduct an undue amount of experimentation to see if the instant method of enhancing a chemical reaction of a molecule would indeed work for any chemical reaction and any molecule.

Genetech, 108 F.3d at 1366 states that “a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion” and “patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable.”

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim is drawn to proteases and recites *S. aureus* as a protease. *S. aureus* is a bacterial species and not a protease. The Examiner has no idea what a V8 protease means. The Examiner notes that endoproteinase Glu-C from *S. aureus* V8 can be obtained from Sigma Aldrich (see attached reference). It also appears as if a comma should be inserted after chymotrypsin and Lys-C as they are different proteases.

Claims 20 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. “Favorable chemical property” is indefinite because it is unclear to the Examiner the exact nature of the chemical property and from which perspective it might be favorable or unfavorable. Claim 21 is rejected as indefinite because it is dependent on an indefinite base claim. The Examiner will examine the claim as it reads on solubility as a chemical property.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

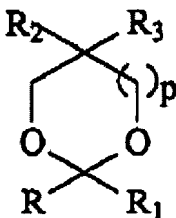
A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-9, 11, 20-30 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Lee et al. (WO 00/70334).

Lee et al. disclose in claim 27:

**27. A method of solubilizing a substance comprising contacting a substance with a surfactant represented by the formula (Formula I):**



**in which**

**p is 0, 1 or 2;**

**R is alkyl;**

**R<sub>1</sub> and R<sub>2</sub> are each, independently, hydrogen or methyl; and**

**R<sub>3</sub> is selected from -OSO<sub>3</sub><sup>-</sup>, -R<sub>4</sub>OSO<sub>3</sub><sup>-</sup>, -R<sub>4</sub>OR<sub>5</sub>SO<sub>3</sub><sup>-</sup>, and -OR<sub>5</sub>SO<sub>3</sub><sup>-</sup>,**

**wherein R<sub>4</sub> and R<sub>5</sub> are each, independently, lower alkyl.**

It is the Examiner's position that "solubilizing a substance" reads on "enhancing a chemical

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reaction of a molecule” as recited in instant claim 1 and is a favorable chemical property with increased efficiency thus anticipating instant claims 20 and 21. Instant claim 25 is anticipated when  $R_2 = H$  and  $p = 0$ . Instant claim 26 is anticipated when  $p = 1$ ,  $R_2 = H$ ,  $R_3 = -OR_5SO_3^-$ ,  $R =$  alkyl and  $R_1$  is methyl (Page 12, Scheme 1). Instant claim 27 is anticipated when  $p = 0$ ,  $R_1 =$  methyl,  $R =$  alkyl,  $R_2 = H$  and  $R_3 = -R_4OSO_3^-$  (Page 12, Scheme 1). Lee et al. disclose wherein the substance is an inclusion body, lipophilic protein or membrane-bound protein sample (Claims 28-31). Lee et al. teach a method where a proteolytic protein (lysozyme, trypsinogen, pepsin, for example) is contacted with ALS-I thus reading on instant claims 2, 6 and 7 (page 14, lines 5-15). The presence of a biomolecule in the aqueous surfactant solution makes it a biological sample and reads on instant claim 4. The aqueous surfactant solution has water, which is a biological fluid and reads on instant claim 5. Samples were heated to ensure protein denaturation (page 14, lines 14-15). Gels were run in the absence of SDS thus reading on instant claim 30 and 33 (page 14, lines 26-31). Lee et al. teach 50  $\mu L$  aliquots and thus perform under microscale conditions and reads on instant claim 29. Mass spectrometry was used for detection of myoglobin treated with ALS-I thus anticipating instant claims 3, 8 and 28 (page 15, lines 4-22). Lee et al. state that “mass spectrometric detection” refers to Matrix Assisted Laser Desorption Ionization MALDI which applicant states on page 21 lines 21-22 is surface desorption ionization analysis and reads on instant claim 9 (Page 6, lines 30-32). Gels run with ALS-I were stained with zinc-imidazole (page 14, lines 26-31). On one hand, the surfactant was degraded in glacial acetic acid for 16 prior to mixing with myoglobin and on the other hand trifluoroacetic acid was added to degrade the surfactant before electrospray mass spectrometry of

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myoglobin and reads on claims 11, 23 and 24 (page 15, lines 10-22; page 16, line 8 and page 18, lines 14-26).

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-9, 11-30 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. (WO 00/70334) in view of Zee-Yong et al. (Anal Chem. 2001, 73, 2558-2564) and Nelson (US 6,093,541).

Applicant claims a method for enhancing a chemical reaction of a molecule comprising contacting the molecule with a surfactant. Please note that with respect to the scope of enablement rejection above, this rejection applies to the scope that is enabled; namely a method of enhancing the solubility of the proteins BSA, lysozyme, ovalbumin, myoglobin, ubiquitin and bacteriorhodopsin.

**Determination of the scope and content of the prior art**

**(MPEP 2141.01)**

The reference of Lee et al. is described in detail above and that discussion is hereby incorporated by reference.

Zee-Yong et al. teach identification of individual proteins (11 proteins were studied and include: rabbit phosphorylase, bovine serum albumin, chicken egg ovalbumin, rabbit aldolase, bovine carbonic anhydrase, horse myoglobin, bovine hemoglobin, horse cytochrome c, chicken egg lysozyme, and bovine ubiquitin (Page 2559 Experimental section).) in complex protein mixtures by MALDI mass spectrometry (Abstract). Thermal denaturation followed by in-solution trypsin digestion is used to achieve uniform digestion of the constituents of the protein mixture (Abstract and page 2559, experimental section).

Nelson teaches proteases for use in mass spectrometers (Abstract and column 7, lines 28-65 and claim 4). Nelson teaches chymotrypsin, Glu-C, Lys-C, S. aureus V8 protease, clostripain, and trypsin, for example, as enzyme proteases and chemical agents such as cyanogens bromide and hydroxylamine (column 7, lines 28-65). Nelson teaches immobilized proteases (Figures 3, 3A, 5 and 6; and column 16, example 10 for example). Nelson teaches adding reducing agents (column 7, lines 55-57).

**Ascertainment of the difference between the prior art and the claims**

**(MPEP 2141.02)**

1. Lee et al. do not expressly teach a method wherein the reaction comprises chemical digestion/chemical alteration and wherein the biomolecule is contacted with a protease; that is immobilized.

2. Lee et al. do not expressly teach a method wherein the method further comprises separating the resulting biomolecule fragments.

### **Finding of prima facie obviousness**

#### **Rational and Motivation (MPEP 2142-2143)**

1. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to perform chemical digestion/chemical alteration or contact the biomolecule with a protease that is immobilized, as suggested by Zee-Yong et al. and Nelson, in the method of Lee et al. and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Zee-Yong et al. and Nelson teach common reagents and techniques known to one of ordinary skill in the art used in the analysis of proteins using mass spectroscopy.

2. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to separate the biomolecule fragments after contacting the biomolecule with a protease, CNBr or hydroxylamine and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because after the chemical digestion, the fragments would be run on the mass spectrometer and separated for identification.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976).

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2-7, 22, 23, and 25-27 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 3, 5-7, 16, 18 and 27 of copending Application No. 10/169,002. Although the conflicting claims are not identical,

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they are not patentably distinct from each other because the instant method of enhancing a chemical reaction of a molecule comprising contacting the molecule with a surfactant is encompassed by the copending claims drawn to a method for performing electrophoresis comprising contacting a sample with the same surfactant as instantly claimed as well as the method of solubilizing a substance comprising contacting the substance with the same surfactant as instantly claimed (copending claims 1 and 27). Copending claim 27 recites inclusion bodies, lipophilic proteins, receptors, membrane bound proteins and biological tissues which reads on instant claims 2, 4-7. Copending claim 18 is drawn to mass spectrometric detection. Copending claims 2 and 3 recite degrading the surfactant by contacting it with an acidic solution which reads on instant claims 23 and 24. The surfactants in copending claims 1, 5-7 and 27 read on instant surfactants in claims 1 and 25-27. One of ordinary skill in the art would have recognized the obvious variation between the instant invention and the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. Please note that a notice of allowance for 10/169,002 has been filed on 2/6/07 but the patent has not yet been issued.

*Conclusion*

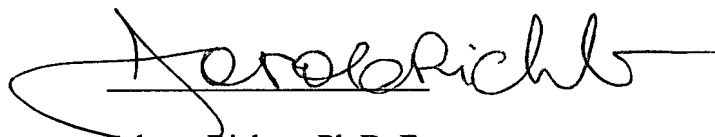
No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ernst V. Arnold whose telephone number is 571-272-8509. The examiner can normally be reached on M-F (6:15 am-3:45 pm).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ernst Arnold  
Patent Examiner  
Technology Center 1600  
Art Unit 1616

A handwritten signature in black ink, appearing to read 'Johann Richter', with a large, sweeping initial 'J' and a horizontal line extending from the end of the signature.

Johann Richter, Ph.D. Esq.  
Supervisory Patent Examiner  
Technology Center 1600

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